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Determining How Gender Affects the Course of Schizophrenia

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A number of gender differences have been reported in schizophrenia.
Do they reflect the general evolution of male/female difference, or are they specific to schizophrenia?
Onset Age

- Earlier in males by a year or so at peak
- Not universally found
- No difference in familial schizophrenia
- No difference in offspring of older fathers

2nd peak around menopause found only in women
Explanations for 2\textsuperscript{nd} Peak

• Estrogen withdrawal?

Or withdrawal of social supports in older age, making older, single women relatively friendless, more like men?
Explanation for Early Onset in Males: Trauma?

- Schizophrenia in men often associated with obstetric injury, early head trauma

More exposed
Both brain symmetry (women’s brains are more symmetric) and sex hormones play a role in the inflammation, immunity, damage, and repair response to injury. This has been shown in Animal Models.


Another explanation – male exposure to toxic substances


“Long-term cannabis use can double risk of psychosis” – Reuters, March 2010
The rate of cannabis use by women has been increasing in recent decades.
Newer Trends in Studying Gender Differences
Animal Models

• Frequently used to study gender differences - because can be experimentally manipulated
• There are pharmacological, genetic, and neurodevelopmental animal models for schizophrenia
• None are perfect.

Humans: Starting Early

Diagram showing the progression of a psychotic episode:
- Early signs of risk
- Prodrome
- Psychotic episode
- Recovery

Vertical axis: Functional Capacity
Horizontal axis: Time


Symptom differences suggest that schizophrenia women are like other women – more affect, more magical thinking
Hormone Studies, in both animals and humans, are becoming more sophisticated

- Arad M, Weiner I. Fluctuation of latent inhibition along the estrous cycle in the rat: modeling the cyclicity of symptoms in schizophrenic women? Psychoneuroendocrinology 2008;33:1401-10
- Czoty et al. Effect of menstrual cycle phase on dopamine D2 receptor availability in female cynomolgus monkeys. Neuropsychopharmacology 2009; 3., 548–54
- Dreher et al. Menstrual cycle phase modulates reward-related neural function in women. PNAS 2007; 104: 2465-2470
- Rubin LH. et al. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr Res. 2010 Oct 12. [Epub ahead of print]
Some Results

- Psychotic symptoms vary over menstrual cycles
- Estrogen enhances neurocognitive performance and attenuates symptoms


Increasingly Studied: Brain Structure
But – Healthy Male/ Female Brain Differences

- the amygdala (larger in males)
- the hippocampus (larger in females)
- the corpus callosum (larger in females)
- women tend to have larger paralimbic and fronto-orbital cortical areas
- men generally have a larger fronto-medial cortex
- sexual dimorphisms have also been reported in the hypothalamus
Is **Attenuation** of Sexual Dimorphism in the brain the hallmark of Schizophrenia?


There are three possible mechanisms through which sex-linked gene expression could contribute to sexual dimorphism in brain and behaviour.

1. 15-25% of all X-linked genes on the human X chromosome may escape X-inactivation.
2. There is also male-limited expression of genes in the non-recombining region of the \textit{Y} chromosome
3. Boys inherit their sole X from their mother.

Girls inherit from both parents.

Maternal or paternal alleles may be suppressed by genomic imprinting.

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Hunting for genes along the estrogen pathway


Copy number variations (CNVs) at various loci are found in association with mental retardation, autism spectrum disorders, and schizophrenia – neurodevelopmental disorders that affect more males than females or affect males more severely.
Do Sex Differences Affect Diagnosis?

Do Sex Differences Affect Prognosis?


Do Sex Differences Affect Treatment with Antipsychotics?

- Effectiveness and Tolerability in the 2 Sexes
Liver enzymes **CYP3A4, 2D6, CYP1A2** are hormone sensitive
Side Effects women are prone to:

- Osteoporosis
  - Venous Thrombosis
  - Stroke
- Weight
  - Hirsutism, Acne
  - Pulmonary Embolus
  - Venous Thrombosis
  - Stroke
- Diabetes
  - Pregnancy problems
  - Metabolic Syndrome
  - Cardiovascular Disease
- Fertility problems
  - Agranulocytosis
  - Pulmonary Embolus
- Sexual dysfunction
- QTc
- Allergies
  - Breast cancer

Women have more side effects

BUT

° Sex stratification not always done
° Low numbers of women
° Searches can’t be duplicated

Conclusions for Rx - use low doses, avoid polypharmacy – watch for interactions (smoking, contraceptives, coffee)
Conclusions for research - There is an obvious need to improve the methodology

Golder S. et al., Room for improvement? A survey of the methods used in systematic reviews of adverse effects. BMC Med Res Methodology. 2006; 6:3
Do Sex Differences Affect Care Needs?

- Women have more needs in:
  - physical health
  - safety to self
  - child care

Conclusion – Sex/gender differences have important implications for diagnosis, prognosis, treatment and care needs and studying the differences will ultimately help to resolve the puzzle of schizophrenia.